Serum High-Density Lipoprotein Cholesterol and Risk of Non-Hodgkin Lymphoma

Unhee Lim,[1] Travis Gayles,[2] Hormuzd A. Katki,[1] Rachael Stolzenberg-Solomon,[1] Stephanie J. Weinstein,[1] Pirjo Pietinen,[3] Philip R. Taylor,[1] Jarmo Virtamo,[3] and Demetrius Albanes[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, Rockville, Maryland; [2]University of Illinois College of Medicine, Urbana-Champaign, Illinois; and [3]Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki, Finland

Abstract

Lymphoma patients often exhibit abnormal lipid metabolism. Recent evidence, however, suggests that a decrease in circulating high-density lipoprotein cholesterol (HDL-C) may occur during lymphomagenesis, reflecting underlying etiology such as inflammation. We investigated the relationship between prediagnostic HDL-C and non-Hodgkin lymphoma (NHL) in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study cohort. At baseline, serum HDL-C and total cholesterol concentrations from fasting blood, information on diet and lifestyle, and direct measurements of height, weight, and blood pressure were obtained from 27,074 healthy male smokers of ages 50 to 69 years. Cox proportional hazards models with age as underlying time metric was used to estimate relative risks (RR) and 95% confidence intervals (95% CI). We found no association between total or non-HDL cholesterol and the 201 incident NHL cases ascertained during the follow-up (1985–2002), but observed an inverse association between HDL-C and NHL, which changed with length of follow-up. High HDL-C was associated with lower risk of all NHL during the first 10 years (n = 148; RR for 5th versus 1st quintile, 0.35; 95% CI, 0.19–0.62; P_{trend} < 0.0001), but not with diagnoses during later follow-up (n = 53; RR, 1.31; 95% CI, 0.55–3.10). The inverse association was similar for NHL subtypes and was not modified by obesity, blood pressure, physical activity, or alcohol intake, but seemed to be stronger in men with lower duration of smoking ($P_{interaction}$ = 0.06). Our findings implicate HDL-C as a preclinical indicator of NHL and warrant further prospective investigations for its etiologic contribution. [Cancer Res 2007;67(11):5569–74]

Introduction

Non-Hodgkin lymphoma (NHL), a group of heterogeneous malignancies of lymphoid origin, is the neoplasm with the second largest increase in incidence in recent decades (1). Whereas the etiology in general and the reason for the recent increase are still unknown, evidence consistently suggests that chronic stimulation of the immune system, as occurs in autoimmune and chronic inflammatory disorders, increases the risk (2, 3). Furthermore, clinical studies of lymphoma patients have reported lipid abnormalities that are similar to the dyslipidemia observed in inflammatory and infectious diseases (4, 5). In particular, patients similarly show low circulating levels and impaired function of high-density lipoprotein cholesterol (HDL-C; refs. 5, 6). Therefore, low circulating levels of HDL-C in lymphoma patients may occur before the clinical onset of cancer and may serve as a marker for inflammation-induced lymphomagenesis, rather than a consequence of lymphoma-induced acute-phase responses (5).

Despite much epidemiologic research conducted on the relationship between serum total cholesterol and cancer mortality (7), no prospective data exist, to our knowledge, to examine the involvement of HDL-C in lymphomagenesis. In fact, only a few prospective studies of HDL-C have been conducted in relation to incident cancers in general, with most evidence related to breast cancer (8–10). The largest and longest of such investigations found ~25% lower postmenopausal breast cancer risk associated with the highest compared with the lowest quartile of baseline HDL-C, especially among overweight and obese women (10). The study did not detect a parallel positive association between serum total cholesterol and cancer, from which it was speculated that HDL-C specifically may be a marker of cancer risk due to hormonal and metabolic disturbances induced by obesity (10, 11). Obesity is also a putative risk factor for NHL (12–14). In addition, some studies suggest antilymphomagenic effects of lipid-altering drugs (15–17), which may be, in part, mediated through HDL elevation among the users.

To evaluate the etiologic involvement of HDL-C in lymphomagenesis, we investigated the association between prediagnostic serum HDL-C levels and the subsequent development of NHL during ~17 years of follow-up of Finnish male smokers in the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study cohort. We were able to examine any confounding or modifying effects of lifestyle factors that are known to affect HDL-C levels; for example, among healthy people without genetic disorders for HDL-C metabolism, moderate alcohol consumption and physical activity are positive determinants, whereas smoking and obesity are negatively correlated to HDL-C (18–20).

Materials and Methods

Study population. The ATBC Cancer Prevention Study is a prospective follow-up study of participants in a randomized, double-blinded, placebo-controlled, chemoprevention trial (1985–1993) for the efficacy of α-tocopherol or β-carotene supplements in reducing lung and other cancers among smokers. As previously described in detail (21), 29,133 eligible men in southwestern Finland who were of ages 50 to 69 years and smoked at least five cigarettes per day were randomly assigned to receive either active supplements or placebo between April 1985 and June 1988. Exclusion criteria

Note: U. Lim and T. Gayles are co-first authors.

Requests for reprints: Unhee Lim, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, EPS 320, Rockville, MD 20852. Phone: 301-451-9624; Fax: 301-496-6829; E-mail: limu@mail.nih.gov.

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included history of cancer other than nonmelanoma skin cancer or carcinoma *in situ*, severe angina pectoris, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, anticoagulant therapy, other medical problems that might have limited long-term participation, or current use of vitamin E (>20 mg/d), vitamin A (>20,000 IU/d), or β-carotene (>6 mg/d) supplements. The study was approved by the institutional review boards at the National Public Health Institute in Finland and the U.S. National Cancer Institute. All study participants provided written informed consent.

Baseline data collection. During the baseline clinic visits, the men completed questionnaires on demographic characteristics and medical, smoking, and dietary histories. Diet was assessed using a 276-item food frequency questionnaire that queried frequency and portion size of food items consumed during the previous year (22). We calculated total daily intake of food groups and nutrients from the questionnaire responses through linkage with the food composition database of the National Public Health Institute in Finland (e.g., daily alcohol in grams from weekly consumption of beer, wine, and hard liquor). Leisure-time activity was assessed by asking the average activity during the past year and categorized as (*a*) sedentary (e.g., reading, watching television, listening to radio, going to movies), (*b*) moderate (e.g., walking, fishing, hunting, gardening) fairly regularly, and (*c*) heavy (e.g., exercising to keep fit such as running, jogging, skiing, gymnastics, swimming, ball games) fairly regularly. The study staff measured height and weight, which were used to calculate body mass index (BMI; weight divided by height squared) as an indicator of obesity (23), and diastolic and systolic blood pressure using a standardized protocol (24).

Blood lipid measurements. At baseline, the participants also provided an overnight fasting blood sample, and serum specimens were stored at −70°C (25). Cholesterol concentrations were determined enzymatically (CHOD-PAP method, Boehringer Mannheim). HDL-C was measured after precipitation of very-low-density lipoprotein and low-density lipoprotein cholesterol with dextran sulfate and magnesium chloride. Baseline serum cholesterol levels were successfully analyzed in 29,093 men. At the third-year visit, 22,833 participants had an additional fasting blood collection, which was also analyzed for HDL-C and total cholesterol.

Case ascertainment. Incident cancer cases were ascertained between April 1985 and April 2002 by linkage of the cohort participants to the Finnish Cancer Registry, which provides almost 100% case coverage (26). As described earlier (27), we used pertinent histology information (International Classification of Disease-Oncology second edition; ICD-O-2) and the WHO classification (28) to define NHL cases (ICD-O-2 9590–9595, 9670–9677, 9680–9688, 9690–9698, 9700–9715, 9823) and its three main subtypes: diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma combined.

Statistical analysis. Follow-up time for each participant was calculated from the date of randomization until diagnosis of NHL, death, or April 2002. Of 29,093 men with baseline serum cholesterol values, 27,074 had complete dietary and other lifestyle data for covariate adjustments in the analyses. Similarly, of the 22,833 men with follow-up serum HDL-C values, 21,543 had dietary and lifestyle data.

HDL-C was analyzed both as continuous and categorical (quintile) variables based on the distribution in the entire cohort. Baseline characteristics were examined by HDL-C level and by case status to identify potential confounders. General linear model regression was used to estimate age-adjusted means of baseline characteristics for each quintile of HDL-C; trend tests were determined using linear contrasts in the general linear model (Table 1). Wilcoxon rank sum tests (continuous variables) and χ^2 tests (categorical variables) were used to compare unadjusted baseline characteristics of cases to noncase cohort members (data not shown). All foods and nutrients, except alcohol, were adjusted for caloric intake using the nutrient density method (29).

To estimate relative risks (RR) and 95% confidence intervals (95% CI) for the association between HDL-C and NHL, we used Cox proportional hazards models. We first tested the assumption of proportional hazards over the follow-up period with a cross product term between HDL-C and follow-up time in person-years and found a significant interaction ($P_{\text{interaction}} = 0.03$). The approximate time point where the change in the HDL-NHL association occurred was estimated by nonparametric spline of the RR against follow-up time and by Cox regression models that tested the significance of cross product terms of HDL-C with indicator variables for various time points (e.g., follow-up year 1, 2,. . ., 16) while using age as the underlying time metric, both of which indicated the follow-up year 10 as the cutoff point in time. All subsequent analyses were done stratified for the first 10 years versus subsequent follow-up, with age as the time metric.

Effect modification of the HDL-NHL association by other risk factors was evaluated using cross-product terms ($P < 0.10$ was considered significant) and likelihood ratio test statistics comparing models with and without the cross product term. Potential confounding factors were added one at a time to the base model of HDL-C and NHL that adjusted for age as the time metric; factors that changed the risk estimate for HDL-C by >10% were considered confounders. The following factors were evaluated as potential confounders: serum total cholesterol, BMI (four categories of <25, 25–29.9, 30–34.9, 35+), alcohol intake, leisure-time physical activity (three categories of sedentary, moderate, and heavy as described above), study interventions (α-tocopherol and/or β-carotene supplements), family history of cancer, caloric intake, and dietary intake of calorie-adjusted total and saturated fat, fiber, and fish. Dose response (P for linear trend) in the HDL-NHL association was tested using the significance of the continuous HDL-C variable or Wald χ^2 test of a variable consisting of median values of quintiles. All statistical analyses were done using Statistical Analysis Systems (SAS, Inc.) software and two-tailed tests ($\alpha = 0.05$).

Using the R package NestedCohort (R Foundation for Statistical Computing; ref. 30), HDL-C was also analyzed as a time-dependent covariate in the Cox model, accounting for the subjects with missing values of third-year HDL-C by treating the follow-up measurements as being nested within the ATBC Cancer Prevention Study cohort. In addition, R-NestedCohort was used to estimate standardized cumulative incidences of NHL for each quintile of baseline HDL-C and the multivariable-adjusted population-attributable risk if everyone had the NHL risk of those in the 5th quintile of baseline HDL-C.

Results

During up to 17.4 years of follow-up (or 339,475 person-years, with a median of 14.1 years), 201 incident NHL cases were ascertained. Mean HDL-C levels for the cohort at baseline and at 3 years were 46 and 45 mg/dL, respectively, with a high correlation between the two ($r = 0.77$). Age-adjusted baseline characteristics, including known determinants of HDL-C and putative risk factors for NHL, were examined across increasing levels of HDL-C (Table 1). Men in higher quintiles of HDL-C tended to be thinner and consumed more alcohol. Compared with cohort members without NHL, cases were slightly older, had smoked longer, and consumed slightly less alcohol and fish (data not shown).

We found a significantly different association between HDL-C and NHL in the first 10 years versus subsequent follow-up ($P_{\text{interaction}} = 0.03$). In stratified analyses based on the two follow-up phases, baseline HDL-C was inversely associated with NHL risk during the first 10 years of the follow-up but showed no association later in follow-up (Table 2). During the first 10 years of follow-up, each 5 mg/dL increase in HDL-C was associated with a 15% reduction in risk of NHL. Alternatively, participants with ≥55 mg/dL HDL-C had ~65% lower risk of developing NHL compared with those with <36 mg/dL. RRs for increasing HDL-C deciles compared with the lowest decile were 0.90, 0.81, 0.68, 0.44, 0.73, 0.53, 0.47, 0.36, and 0.29. Figure 1 depicts the association in 2-year intervals of follow-up: the first 2 years yielded a significant inverse association between HDL-C and NHL followed by associations of diminishing magnitude for up to 10 years and null associations thereafter. Baseline total and non-HDL cholesterol (calculated by subtracting HDL-C from total cholesterol) were not associated with NHL and did not affect the HDL-NHL associations. A separate analysis of

HDL-C and total cholesterol at 3 years yielded similar findings of an inverse HDL-NHL association only in the first 10 years and a null association between total or non-HDL cholesterol and NHL (data not shown).

When baseline HDL-C and change in HDL-C at 3 years of follow-up were modeled simultaneously, risk estimates for baseline HDL-C remained similar (Table 2). An actual increase in HDL-C by 5 mg/dL in the 3 years was associated with a 17% reduced risk of NHL during the early follow-up (3–10 years), which was similar to the estimation made using baseline HDL-C. Alternatively, compared with HDL-C reduction by ≥3 mg/dL during the first 3 years, a small change and an increase by ≥3 mg/dL were associated with a lower risk of subsequent NHL only during the early follow-up, with RRs of 0.65 and 0.50, respectively (Table 2). When HDL-C was analyzed as a time-dependent covariate in a nested study to account for missing values at 3 years, the inverse HDL-NHL association was strengthened (RR for highest versus lowest quintile, 0.22; 95% CI, 0.10–0.47).

The inverse association during the early follow-up was moderately different by cumulative years of smoking ($P_{interaction}$ = 0.06): it was stronger among men with fewer self-reported years of smoking (≤36 years; RR for HDL-C of 5th versus 1st quintile, 0.13; 95% CI, 0.04–0.44) than those with longer smoking history (RR, 0.58; 95% CI, 0.29–1.15). Other risk factors, including levels of BMI (<25 versus ≥25 kg/m^2), blood pressure (diastolic >85 mm Hg or systolic >130 mm Hg as defined for metabolic syndrome; ref. 31), leisure-time physical activity (three categories), and alcohol consumption did not modify the association (data not shown). Among potential confounders examined in Table 1 and intervention supplements, only alcohol intake slightly attenuated the HDL-NHL association and had therefore been included in all models.

In the NHL subtype analyses stratified by follow-up time, HDL-C >55 mg/dL was associated with nonsignificantly decreased risk of diffuse large B-cell lymphoma (n = 44; RR, 0.56; 95% CI, 0.19–1.65), follicular lymphoma (n = 13; RR, 0.28; 95% CI, 0.03–2.75), and chronic lymphocytic leukemia/small lymphocytic lymphoma (n = 50; RR, 0.54; 95% CI, 0.22–1.30) only during the first 10 years of follow-up. The proportions of three main subtypes diagnosed in early versus later phase of the follow-up were similar.

Discussion

Our findings provide the first prospective evidence that high HDL-C is associated with low risk of developing NHL in a dose-responsive manner. The association was strongest in the first 4 years of follow-up, but remained inverse for up to 10 years and was similar for all three main NHL subtypes.

Table 1. Baseline age-adjusted characteristics (means or proportions) by serum HDL-C quintiles; ATBC Cancer Prevention Study cohort, 1985–2001 (N = 27,074)

Characteristics	Serum HDL quintile (mg/dL)				
	1 (<36.0)	2 (36.1–41.7)	3 (41.8–47.2)	4 (47.3–55.3)	5 (≥55.4)
Serum lipids (mg/dL)					
HDL-C	32	39	44	51	65
Total cholesterol	238	243	243	242	241
HDL-C at 3-y follow-up	33	39	44	49	59
HDL-C change in first 3 y	1.5	0.3	−0.6	−1.7	−5.6
Age (y)	57.2	57.2	57.3	57.1	57.1
Smoking history					
cigarettes/d	21	20	20	20	21
Years smoked	36	36	36	36	36
Education (%)					
Elementary school or less	77	78	79	78	79
Up to junior high school	15	14	14	14	13
≥High school	7	8	7	8	8
Blood pressure (mm Hg)					
Diastolic	88	88	87	87	88
Systolic	142	142	141	142	143
BMI (kg/m^2)	28.0	27.1	26.5	25.5	24.4
Leisure-time physical activity					
Sedentary	45	41	40	39	42
Moderate	50	53	53	55	52
Heavy	5	6	7	7	6
Alcohol consumption (g/d)	12	15	17	19	26
Total energy (kcal/d)	2,776	2,827	2,834	2,829	2,811
Dietary intake (g/1,000 kcal/d)					
Fat	75	81	74	77	77
Fiber	9	9	9	9	9
Fish	15	14	14	14	15

NOTE: General linear model regression was used to estimate age-adjusted means or proportions of variables for each quintile of baseline HDL-C.

Table 2. Adjusted RRs and 95% CIs for NHL according to baseline serum cholesterol (HDL-C) quintiles and 3-y change in HDL-C stratified by follow-up time; ATBC Cancer Prevention Study cohort, 1985–2001 (N = 27,074)

HDL-C	Early follow-up (≤10 y)		Early follow-up (3–10 y)*		Late follow-up (>10 y)*	
	Case	RR (95% CI)	Case	RR (95% CI)	Case	RR (95% CI)
Baseline, continuous (5 mg/dL increments)	148	0.85 (0.78–0.92)	111	0.85 (0.78–0.94)	53	1.01 (0.90–1.14)
Baseline, quintiles						
<36 (mg/dL)	44	1.00	27	1.00	10	1.00
36.1–41.7	36	0.78 (0.50–1.22)	30	0.99 (0.59–1.66)	9	0.83 (0.34–2.05)
41.8–47.2	28	0.62 (0.39–1.01)	22	0.71 (0.40–1.26)	13	1.24 (0.54–2.85)
47.3–55.3	24	0.52 (0.32–0.87)	18	0.55 (0.30–1.00)	8	0.74 (0.29–1.90)
55.4+	16	0.35 (0.19–0.62)	14	0.38 (0.20–0.75)	13	1.31 (0.55–3.10)
P_{trend}		<0.0001		0.0008		0.56
Change, continuous (5 mg/dL increments)			111	0.83 (0.71–0.95)	53	1.09 (0.84–1.41)
Change, categorical						
Decrease by >3 mg/dL			62	1.00	26	1.00
Change ≤3 mg/dL			33	0.65 (0.42–1.01)	13	0.72 (0.36–1.43)
Increase by >3 mg/dL			16	0.50 (0.29–0.87)	14	1.19 (0.61–2.30)

NOTE: Cox proportional hazards regression was done with age as the underlying time metric, adjusting for serum total cholesterol and alcohol intake at baseline.

*Risk estimates for baseline HDL-C (continuous or quintile categories) were adjusted simultaneously for change in HDL-C (three categories). Alternatively, estimates for change in HDL-C (continuous or three categories) were adjusted for baseline HDL-C. Cases that occurred during the first 3 y (n = 37) were removed from the early-phase estimation for the mutually adjusted analyses.

The inverse HDL-NHL association was attenuated as follow-up increased, which is consistent with a HDL-lowering effect of latent lymphoma (4). Although our findings may not provide conclusive evidence either for or against such latency effects, specific aspects of the analyses support the hypothesis that the HDL-NHL association may reflect underlying lymphomagenesis, such as chronic inflammation. The inverse relationship was sustained for a substantial length of time after baseline (i.e., 10 years). Consistent risk estimates were obtained from the comparison of high versus low baseline HDL-C and from the comparison of actual increase versus decrease in HDL-C during the follow-up. In addition, risk estimates were similar for aggressive (diffuse large B-cell lymphoma) and some of the more indolent subtypes (chronic lymphocytic leukemia/small lymphocytic lymphoma), contradicting a contribution of strong detection bias due to commonly asymptomatic disease. No association was detected for baseline total or non-HDL

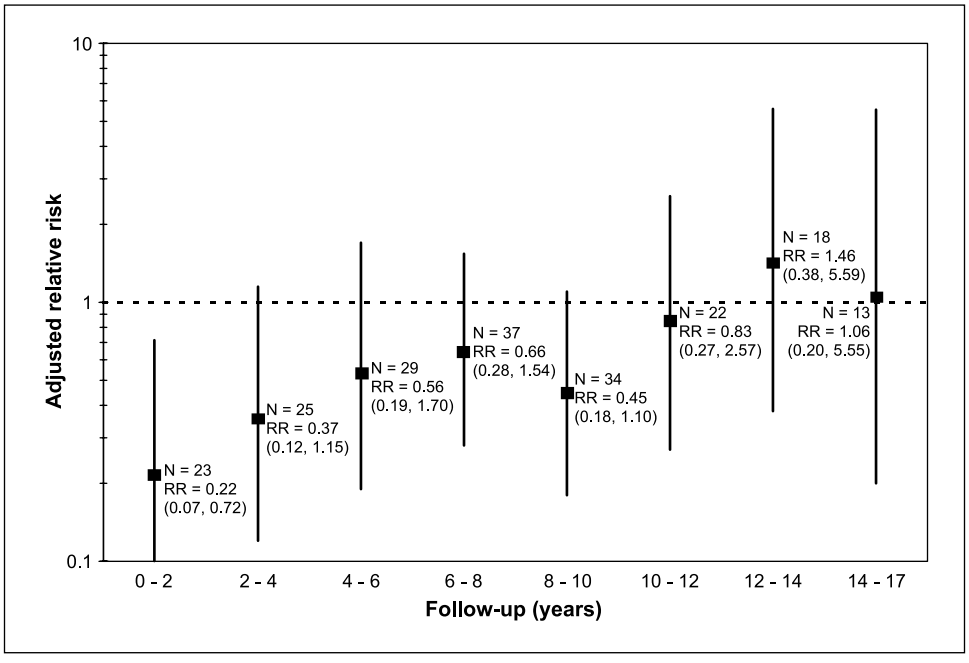

Figure 1. RR of NHL comparing HDL-C >47.2 mg/dL with HDL-C <36 mg/dL over follow-up time. Cox proportional hazards model adjusting for age, serum total cholesterol, and alcohol at baseline was applied to sequential 2-y follow-up periods to construct the figure, depicting RRs (closed square) and their 95% CIs comparing 4th and 5th quintiles combined versus 1st quintile of HDL-C.

cholesterol and NHL, which further suggests that our findings did not result from systematic abnormalities in lipid metabolism often observed in cancer patients (5, 7, 32–34).

Epidemiologic studies of chronic immuno-inflammatory conditions, treatments, and relevant genetic susceptibility suggest their involvement in lymphomagenesis (2, 3, 35). Chronic inflammation is known to reduce both serum HDL-C concentrations and its anti-inflammatory properties (36, 37). Low HDL-C, therefore, may be a marker for the severity of systemic inflammation and inflammation-induced NHL risk. On the other hand, high HDL-C itself may be protective against NHL. HDL-C seems to modulate inflammatory responses independent of non-HDL cholesterol levels (38) by inhibiting cytokine-induced expression of endothelial cell adhesion molecules and by suppressing chemotactic activity of monocytes and lymphocytes (39, 40). In addition, HDL-C may protect the integrity of lymphocytes from oxidative damage (41, 42). If HDL-C is indeed a risk factor for NHL, our findings suggest its population-attributable risk to be ~46% (95% CI, 14–66%). However, our observation of a diminishing association with follow-up time calls for caution in its causal interpretation. The attenuation may be, in part, due to within-person variability in HDL-C over time (43) and decreasing predictability of a single baseline measure.

Of limited prospective data on HDL-C and cancer incidence (8–10, 44), a large and extended follow-up of Norwegian women observed a significant inverse association between baseline HDL-C and postmenopausal breast cancer, especially among overweight and obese women (10). In the ATBC Cancer Prevention Study, we had baseline measurements of three of five indicators of metabolic syndrome (31), HDL-C, obesity, and blood pressure, but not serum triglycerides or glucose. We did not observe any effect modification by obesity or blood pressure of the HDL-NHL association. It is plausible, however, that we could not detect a modifying effect due to heavy smoking history of our study participants [e.g., because smoking is associated with lower BMI (although the average BMI was 26.3 kg/m^2)]. That the HDL-C association was more apparent among smokers with less cumulative exposure is consistent with this and could have resulted from greater effect of HDL-C against lymphomagenesis among people with lower inflammatory or oxidative burdens from smoking (45).

Our study has several strengths that contribute to the validity of the findings. They include a long prospective follow-up, thorough case ascertainment with histologic information for subtype classification, detailed data on relevant lifestyle factors, and direct measurements of blood pressure and anthropometry that would have minimized any bias from self-report. We observed good internal consistency in comparing estimated effects associated with a 5 mg/dL increase in baseline HDL-C (RR, 0.85) versus actual change during the first 3 years (RR, 0.83). HDL-C and total cholesterol were measured in fasting blood, reducing postprandial variability (although HDL-C is known to be affected minimally by meal intake compared with some of non-HDL cholesterol fractions; ref. 46). HDL-C levels in our study population were comparable to those in the U.S. population with mixed smoking history: low HDL-C (<40 mg/dL) was observed in 35% of the ATBC Cancer Prevention Study participants versus 33% among U.S. men (47).

By nature of the observational design, we cannot preclude residual confounding by other risk factors. Our observations were limited to smokers, which may compromise generalizability to never or former smokers. We found little change in the HDL-NHL association with adjustment for smoking, which is consistent with our current understanding of smoking not being a critical risk factor for NHL other than follicular lymphoma subtype (48). However, we detected a stronger protective association among men who smoked fewer years, which may imply more relevance of our finding to never and former smokers. We did not have information on history of chronic inflammatory conditions or autoimmune diseases, which could have been examined for the hypothesis that the inverse HDL-lymphoma association reflects underlying etiology related to chronic immune stimulation, and we did not measure subfractions of highly heterogeneous HDL-C particles (36, 49), the comparison of which in early versus late follow-up could have been examined for further evidence of HDL-C involvement.

Our findings need to be replicated in other populations, including women and nonsmokers. Specifically, given the time interaction we observed, prospective studies with repeat measures of HDL-C as well as other biomarkers of putative mechanisms may provide more insight into the hypothesis that low HDL-C may serve as a screening tool among high-risk individuals, such as patients of chronic inflammatory conditions, or for prognostic monitoring of indolent diseases. With these caveats in mind, the potential role of HDL-C as an early indicator or even as an etiologic factor of NHL would be of substantial importance to public health considering the high prevalence of low HDL-C in developed countries.

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